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AG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Vera Afremova
Art Unit	:	1651
Appellant	:	John Ernest Hart
Serial No.	:	09/856,944
Filed	:	May 30, 2001
Confirm. No.	:	6466
For	:	Isolated Material Having an Anti-Organotrophic Effect

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SUBSTITUTE APPEAL BRIEF

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I. REAL PARTY IN INTEREST

This application is owned by Endocrine Pharmaceuticals Limited.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

Claims 1, 3-6, 8 and 11-14 are pending in this application and stand finally rejected under 35 U.S.C. §103(a). Claims 1, 3-5, 8 and 11-13 stand rejected under 35 U.S.C. 102(b) as anticipated by U.S. Patent No. 4,734,398, or, in the alternative, under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 4,734,398. Also, claims 1, 3-6, 8 and 11-14 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 4,734,398. The §102/§103 rejections of claims 1, 3-5, 8 and 11-13, as well as the §103 rejections of claims 1, 3-6, 8 and 11-14 are appealed herein.

IV. STATUS OF AMENDMENTS

In an Amendment dated September 10, 2004, the Applicants canceled claims 2, 7, 9-10, 16 and withdrew claims 15, 17-21. The September 10, 2004 Amendment was entered leaving claims 1, 3-6, 8 and 11-14 pending. In the final Office Action dated November 24, 2004, claims 1, 3-6, 8 and 11-14 were finally rejected. The claims as currently pending are attached hereto in Appendix A.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The subject invention, as set forth in claims 1 and 3-6, is an endogenous material, inducible in a mammal post-oestrus by clomiphene, and having the ability to reduce the mass of body organs including non-gonadal organs, of a live adult mammal, the material being obtained by:

collecting ovarian venous blood from a female mammal post-oestrus;

preparing ovarian venous plasma from the blood; and

at least partially purifying said material from the plasma to obtain at least a nominal 10-30 kD sub-fraction (see page 1, lines 20-33 as well as page 2, lines 24-26 of the specification as filed).

A further aspect of the invention, as set forth in claims 8 and 11-14, is a pharmaceutical composition that comprises the material as set forth in claim 1 (see, for example, page 4 lines 12-19).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Claims 1, 3-5, 8, 11-13, which are directed to a material that reduces the mass of body organs, including non-gonadal organs of a live adult mammal, and that is inducible by clomiphene and obtained by purifying post-oestrus ovarian venous blood, have been rejected under 35 U.S.C. §102(b) as being anticipated by, or obvious in view of, U.S. Patent No. 4,734,398.

B. Claims 1, 3-6, 8, 11-14, which are directed to a material that reduces the mass of body organs, including non-gonadal organs of a live adult mammal, and that is inducible by clomiphene and obtained by purifying post-oestrus ovarian venous blood, have been rejected under 35 U.S.C. §103(a) as being obvious in view of U.S. Patent No. 4,734,398 .

VII. ARGUMENT

A. Claims 1, 3-5, 8, 11-13, which are directed to a material that reduces the mass of body organs, including non-gonadal organs of a live adult mammal, and that is inducible by clomiphene and obtained by purifying post-oestrus ovarian venous blood, are not anticipated by, or obvious in view of U.S. Patent No. 4,734,398, which describes a material having a similar molecular weight but which is obtained from a different source and has different properties.

The subject invention is a unique and advantageous material that reduces the mass of non-gonadal organs in live adult mammals. This material, which is inducible by clomiphene, is found in a purified 10-30 kD sub-fraction of mammalian ovarian venus blood collected post-oestrus.

The Appellant has claimed this material in terms of its molecular mass, its source, and its salient biological properties. In rejecting the Appellant's claims, the Final Office Action cites a single reference — the diZerega reference. The diZerega reference discloses a material whose molecular mass falls within the range set forth in the Appellant's claim; however, the diZerega material does not possess multiple other characteristics of the Appellant's claimed material. These additional characteristics provide a definite characterization of the claimed material such that it can be readily distinguished from the diZerega material.

As discussed below, because the diZerega material does not possess (explicitly or inherently) the characteristics set forth in the Appellant's claims, a finding of novelty for the Appellant's claims is compelled. Furthermore, there is no teaching, guidance, or suggestion in the diZerega reference as to how one skilled in the art would arrive at the Appellant's material. Therefore, the Appellant's material, as claimed, is also non-obvious in view of diZerega.

The Appellant's claims have several very specific limitations that are not met by the diZerega reference. Each of these limitations is discussed below:

1. The material must be inducible post-oestrus by clomiphene.

Clomiphene is a well-known non-steroidal ovulatory stimulator. Although clomiphene is known to stimulate ovulation in humans when administered under certain conditions, in the current case the claimed material has been found to be induced by clomiphene independent of ovulation. This limitation is set forth in the claim by reciting that the claimed material is inducible "post-oestrus" by clomiphene and is obtained in post-oestrus ovarian venous blood. Because clomiphene does not re-induce ovulation, it is clear that the presence of the claimed material in post-oestrus ovarian blood is not a consequence of ovulation.

In an Office Action dated May 13, 2004 the examiner states at page 7 that "the claimed invention encompasses a material that is required to be isolated from ovarian venous blood of a mammal that is in the phase of ovulation or that is induced to ovulate by clomiphene."(emphasis added) This statement incorrectly characterizes the current invention because, as required by the claims, the claimed material must itself be inducible by clomiphene post-oestrus.

As explained in Prof. Clarke's Expert Declaration dated 26 July 2004, the Appellant's claimed material (a.k.a. "micrin") is induced by clomiphene at any time during the oestrus cycle and the induction of the claimed material is not caused by ovulation:

> 6. Clomiphene is known to induce ovulation, if provided over a prolonged period of time, in women who are not ovulating. However, if sheep are provided with an acute administration of clomiphene within a few days after ovulation has occurred, as described in the present patent application, this certainly does not cause further ovulation. The reproductive system is refractory to re-ovulation induction at this time, because the sheep would be in the luteal phase of the oestrous cycle, when progesterone levels are high; this prevents ovulation.
>
> • • •
>
> 8. On the other hand, clomiphene does appear to induce the production of micrin, at whatever phase of the oestrous cycle it is administered. Micrin induction by clomiphene does not appear to be a secondary effect of ovulation, as it occurs whenever clomiphene is administered and regardless of when ovulation has occurred.

Therefore, because administration of clomiphene post-oestrus does not induce re-ovulation, the Appellant's material, which is found in post-oestrus blood after administration of clomiphene, is clearly directly inducible by clomiphene.

In addressing Prof. Clarke's Expert Opinion as it relates to this claim limitation, the Final Office States at page 7:

> [t]he characteristics of the claimed compound and/or feature of the claimed invention such as being inducible by clomiphene and/or collection from post-oestrus female mammals do [sic] appear to be critical and distinguishable features of the claimed invention over the prior art since the prior art material is collected around ovulation time and, thus, it would be induced by clomiphene that induces ovulation and/or because the cited material(s) or materials with 10-20 kD would be present or collected in a least some amounts in female mammal post-oestrus or after ovulation.

To the extent that this sentence/paragraph is comprehensible at all, it is technically inaccurate (because clomiphene does not induce ovulation post-oestrus) and certainly does not provide any sound basis for concluding that diZerega teaches a material that is inducible post-oestrus by clomiphene.

2. The claimed material reduces the mass of organs, including non-gonadal organs, of a live adult mammal.

This claim limitation has three aspects: a) a reduction of organ mass, b) including non-gonadal organs, and c) in live adult mammals. The diZerega reference does not teach any of these aspects. Each of these three claim limitations is addressed in detail below.

a. Reduction of organ mass

The Final Office Action incorrectly states (at, for example, page 2) that diZerega's FRP "has the ability to reduce organ mass". diZerega's FRP does not cause weight reduction of anything, in absolute terms; it merely suppresses a weight gain that would otherwise have occurred in a particular experimental situation involving ovarian enlargement. On those occasions where diZerega uses phrases that could be construed as indicating a true decrease in ovarian weight (e.g. column 10 line

48), diZerega is clearly using this language to refer to a decrease in the increase that would otherwise have occurred. This is evident from a reading of the description (rather than picking out a phrase in isolation), and is also evident from the numerical values given for ovarian weight.

In considering this issue from the perspective of one skilled in the art, it is first necessary to understand the experimental test protocol that diZerega was using. This is explained in detail starting at column 9 line 50 to column 10 line 33. The biological assay used 23-day- old immature rats that were initially subjected to hypophysectomy – that is, removal of the pituitary – and then given an implant containing DES. A well established effect of hypophysectomy is a reduction in ovarian mass, as is reported in Hart ("Pituitary-related weight changes affecting the liver, uterus and adrenal glands of rats treated with hexoestrol and clomiphene in high doeses" (1990) *Toxicology* 61:185-194). This effect is due to the absence of pituitary gonadotropins. Forty-eight hours after hypophysectomy, diZerega gave the rats varying concentrations of gonadotropins (such as hMG) and in some cases test fractions, and 24 hours later the animals were sacrificed and the ovaries weighed. Figure 1 shows how the ovarian weight changed in response to hMG. The initial weight was 21.2 mg, and this was seen to increase with the dose of gonadotropin to a maximum of 46 mg. Having carried out this preliminary test, "[o]ne international unit of hMG injected every 12 hours for two days was chosen as the challenge regimen in the bioassay." (column 10 lines 27-30)

Example 1 relates to the identification of FRP from ovarian venous blood taken during the preovulatory stage (column 8 lines 63-67 and column 9 line 13, and column 10 line 35). This blood was treated to select FRP by various steps including eluting fractions, and the fractions were tested in the bioassays. "When these eluents were tested in the bioassays, the combined rat ovarian weights ranged from 57-100 mg . . . fractions with a Ve/Vo of 1.42-1.55 corresponded to an inhibition of hMG-induced ovarian stimulation in the bioassay, as evidenced by a decrease in ovarian weight (59 mg)..." (column 10 lines 41-48). (emphasis added) The emphasized phrase is the one quoted by the examiner, yet it is clear that there is no actual decrease in ovarian weight (59 mg for two ovaries is more than double the initial weight of 21.2 mg). This phrase merely highlights that hMG-induced ovarian stimulation (which, as shown in figure 1, leads to an ovarian weight gain) has been inhibited – consequently the ovarian weights increase by less than they would have done without the FRP.

That is to say, the weight increase (which in Example 1 had gone from 21.2 mg up to 46 mg for each ovary) is decreased.

In the rest of that paragraph there is similar inconsistency in phraseology, although the meaning remains clear:

> Peripheral and ovarian venous blood... demonstrated similar G-50 elution profiles ... However, when ... tested by bioassay, no reduction in ovarian weight ... was found. Further, ovarian venous blood preparations from the anovulatory patients also failed to suppress the response of the ovaries to hMG stimulation. However, ovarian venous sera from the ovulatory ovary of patients 2 and 3 had a similar ... elution profile. Fractions with a Ve/Vo of 1.48-1.60 suppress the response of rat ovarian weight . . . to hMG stimulation ... When active fractions from the G-50 eulents of patients 1-3 were heated or tripsin digested, they lost their ability to suppress ovarian weight ... in response to HMG stimulation." (column 10 line 52 – column 11 line 2)

Figure 3 shows the dose response curve of "ovarian weight suppression" in the DES-treated rat ovaries by fractions from patient 1; again, there is no suggestion that the weights of the ovaries decreased: in every case the values are at least 25 mg (see upper graph), which is greater than the initial weight of 21.2 mg.

Example 2 describes further studies to evaluate the role of FRP. Again, the activity was determined by "inhibition of human menopausal gonadotropin induced ovarian weight gain ... in hypophysectomised, DES-treated, 25 day old female rats." (column 12 lines 13-19). In the Example the material was obtained from human follicular fluid, rather than venous blood. The bioassay procedure is further explained at column 14 lines 1-11:

> "Control determinations (no injected test fractions) for unstimulated ovarian weight were 34.7 mg/rat and for LH-FSH-stimulated were 192 mg/rat ... Where indicated, 100% inhibition equals ovarian weight ... of mean, unstimulated control values. Zero percent inhibition equals ovarian weight...of LH-FSH-stimulated control rats."

Thus, in every case the ovarian weight either remains constant or increases: "100% inhibition" means that the ovarian weight remains at the unstimulated value (34.7 mg per rat [= about 17.3 mg per ovary]).

Example 3 describes further experiments using material obtained from follicular fluid. The bioassay was as described previously, and "[r]esults of control determinations (no injected test

fractions) were 34.8 mg/rat for unstimulated ovarian weight and 122.0 mg/rat for FSH-stimulated ovarian weight" (column 16 lines 39-44).

diZerega himself summarised the findings as: "[i]n Examples One through Three protein(s) in ovarian venous effluent... inhibited rat ovarian weight gain in response to gonadotropin stimulation." [column 20 lines 29-33]. (emphasis added) Thus diZerega's FRP does not have the capability of reducing organ mass; it merely has the capability of inhibiting the increase of ovarian mass as caused by the gonadotropins in the artificial situation of hypophysectomised rats.

The Appellant's claims require the material to cause a decrease in the mass of body organs. This is a very surprising property, and quite different to that of FRP, a local modulator of gonadotropin action. The ability to reduce organ mass is explicitly required by the Appellant's claims; this characteristic is absent from the diZerega teachings.

b. Reduction in mass of non-gonadal organs

After misconstruing diZerega's teachings with regard to FRP's effect on ovaries, the Final Office Action addresses, at page 6 and 7, the ability to reduce mass of non-gonadal organs by stating:

> [a]pplicant also argues that since the combined effect of gonadotropins and "FRP" primary [sic] relates to gonadal organs, there is no reasonable grounds to expect that the cited material {diZerega' compound or "FRP" as argued} would reduce non-gonadal organ mass as the applicant's "micrin" could or would. Although it might be true for chemical compounds established as "FRP" and "micrin", the chemical structure and the link between structure and biological function of the applicant's material is poorly characterized as claimed and as disclosed in order to distinguish the applicant's material from the material(s) as disclosed by the cited diZerega's patent. The only known fact or the only evidence is that structure (molecular weight) of both materials is identical. Therefore, arguments based on some unidentified and/or undisclosed characteristics do not provide sufficient grounds for the evidence to the contrary to the claim rejection under 35 U.S.C. 102(b) . . .

Again to the extent that this is comprehensible at all, the Final Office Action appears, in effect, to ignore this vital limitation completely and simply reiterate that the materials have similar

molecular weights (indeed, going so far as to describe the molecular weights as 'identical', when in each case molecular weights are simply given as falling within a wide range). As to reducing the masses of non-gonadal organs, no data are presented in diZerega relating to the actual reduction of any organ mass, gonadal or non-gonadal. Ignoring a key limitation, non-gonadal action, does not negate its presence in the claim or the failure of the cited reference to disclose a material having this property. Accordingly, a finding of anticipation and/or obviousness is improper.

c. Reduction of organ mass in a live adult mammal.

After careful scrutiny of the Final Office Action, the Appellant has yet to identify where this aspect of the claim is addressed at all. Suffice it to say, diZerega does not teach or suggest a material meeting this claim limitation. diZerega uses non-intact (surgically altered) immature mammals, achieving no reduction in ovarian mass. In contrast, the Appellant's claimed material achieves reduction in ovarian and other organ masses using intact live adult mammals.

3. The material is purified from venous ovarian blood collected from a mammal post-oestrus.

In addressing this issue the examiner makes the following observations:

> "[di Zerega's] [b]lood collection is done on days 12-14 after last menstrual period that is around ovulation period"; (Final Office Action, page 3)

and

> "Furthermore, the starting material of the cited patent is collected about the period of ovulation . . ." (emphasis added) (Final Office Action, page 3)

Perhaps sensing that these statements do not constitute convincing evidence of anticipation or obviousness, the examiner concludes with:

> Or, the starting collected material is considered to be the same regardless cycle timing of ovarian blood collection because the starting collected material would contains at least some amounts of the material(s) as intended whether it is collected during ovulation and post-oestrus. (Final Office Action, page 3)

Again, the Appellant respectfully submits that, to the extent that this statement can be understood at all, it does not provide a basis for concluding that diZerega discloses a material meeting the limitations of the Appellant's claims.

Blood collection for FRP on days 12-14 after the onset of the last menstrual period, as described by diZerega, corresponds to pre-ovulatory sampling, appropriate for a postulated mid-cycle gonadotropin modulator. In contrast, micrin is obtained on day 6 after ovulation (i.e. post-oestrus).

Of course, for an anticipation rejection to be proper, a single prior art reference must disclose, within its four corners, each and every element of the claimed invention. In *Dewey & Almy Chem. Co. v. Mimex Co.*, Judge Learned Hand wrote:

> No doctrine of the patent law is better established than that a prior patent . . . to be an anticipation must bear within its four corners adequate directions for the practice [of the subsequent invention] . . . if the earlier disclosure offers no more than a starting point . . . if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation. 124 F.2d 986, 990; 52 USPQ 138 (2nd Cir. 1942).

The present invention is directed to a material inducible by clomiphene, that reduces organ mass of non-gonadal organs in live adult mammals, and which is obtained post-oestrus. Such a material is not disclosed, or even suggested, by diZerega. Because the diZerega reference does not disclose, within its four corners, a composition having the characteristics recited in the current claims, an anticipation rejection is improper.

With regard to obviousness, the Final Office Action states that even if the claimed material differs from diZerega with regard to some "unidentified characteristics" then:

> . . . the differences between that which is disclosed and that which is claimed are considered to be so slight that the referenced material and/or fractions are likely to inherently possess the same characteristics of the claimed material...(emphasis added) (Final Office Action, page 4)

Of course, "inherency" is a concept most commonly applied in the context of an anticipation rejection. In any event, it is abundantly clear that a rejection based upon inherency (either anticipation or obviousness) is improper in the current case.

Under the Patent Laws, a prior art rejection based on inherency is only proper if the prior art necessarily (not "likely," as stated by the examiner) resulted in the claimed subject matter. *In re King*, 801 F2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). Further,

> the doctrine of inherency is available only when the prior inherent event can be established as a certainty. That an event may result from a given set of circumstances is not sufficient to establish anticipation....A prior inherent event cannot be established based on speculation, or where a doubt exists (emphasis added). *Ethyl Molded Product Co. v. Betts Package Inc.*, 9 USPQ2d 1001, 1032-33 (E.D. KY 1988).

In addressing this issue, Dr. Hart answers relevant questions as follows in his Expert Declaration dated 2 August 2004:

> 5. What if exogenous FRP were given to intact adult mammals, rather than hypophysectomised juvenile animals – would that cause an absolute reduction in ovarian mass? No, all this might achieve would be a blunting of the mid-cycle rise in the mass of the ovulating ovary, given that the mode of action of FRP is to inhibit gonadotropin action. The potential suppression of a rise in mass of the ovulating ovary is not an absolute reduction in the mass of both ovaries, such as can be readily obtained with exogenous micrin.
>
> 6. Would the administration of exogenous FRP to adult intact mammals be expected to cause an absolute reduction in non-gonadal organ masses, as is achieved with exogenous micrin? Again, no. To say otherwise would be to imply that gonadotropins increase the mass of non-gonadal organs, which is not the case, and ignores the fact that FRP does not even reduce in an absolute sense the mass of an ovulatory ovary; diZerega makes it clear (for example column 11, lines 55-66) that the effect of FRP is to suppress the response to gonadatropins.

As discussed above, it cannot reasonably be stated that the diZerega reference discloses or suggests a material that is induced by clomiphene, obtained post-oestrus and that necessarily reduces organ mass (gonadal or non-gonadal) in live adult mammals. The examiner's speculation as to the "likely" properties of the diZerega material is technically incorrect as well as legally insufficient to support a rejection based on the diZerega reference. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102/103 is respectfully requested.

B. Claims 1, 3-6, 8, 11-14, which are directed to a material that reduces the mass of body organs, including non-gonadal organs of a live adult mammal, and that is inducible by clomiphene and obtained by purifying post-oestrus ovarian venous blood, are not obvious over U.S. Patent No. 4,734,398, because the cited reference does not teach or even suggest a material having the advantageous characteristics of the subject material.

Nothing in the diZerega reference would have led the skilled artisan to the advantageous material claimed by the Appellant. As noted above, apart from the molecular mass, no relevant physical or functional similarities exist between the Appellant's material and the composition described in the diZerega reference.

In order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must find both the suggestion of the claimed invention, and a reasonable expectation of success in making and practicing the invention, in light of the teachings of the prior art. *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1531, (Fed. Cir. 1988). The diZerega reference does not disclose or suggest the material claimed by the Appellant.

The claimed material is produced from a different source as follows: FRP activity was detected in ovarian venous blood downstream of ovulatory ovaries, but no FRP activity was found when using peripheral blood or ovarian venous blood from the contralateral anovulatory ovary (see column 10 lines 52-57), nor was there any activity in the case of bilaterally anovulatory patients (see column 10 lines 57-60); in contrast, micrin is found in blood from either ovary and is also detectable in bilaterally anovulatory individuals and in peripheral blood. Micrin is also obtained at a different time during the female reproductive cycle, and has the significantly different property of being able to reduce gonadal and non-gonadal organ size - these all go to show that the present invention is novel and nonobvious, and indeed surprising.

A finding of obviousness is proper only when the prior art contains a suggestion or teaching of the claimed invention. Here, it is only the applicant's disclosure that provides such a teaching, and the applicant's disclosure cannot be used to reconstruct the prior art for a rejection under 35

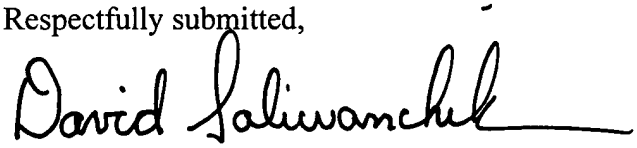
U.S.C. §103. This was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969):

> The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is we must review the prior art without reading into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d 226, 112 USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

The diZerega reference does not disclose or suggest a material that is inducible by clomiphene post-oestrus nor does it disclose a material that can reduce organ mass. Rather, diZerega only provides FRP, a material that is not induced by clomiphene and only appears to affect ovaries in their growth response to gonadotropins. Considering this clomiphene point further, it can be pointed out that diZerega investigated the effect of clomiphene treatment in spontaneously menstruating women, the results being shown in diZerega's figure 18. Neither results shown in the figure (follicular fluid inhibitory protein activity and estradiol concentration) show any significant difference between the untreated women and those treated with clomiphene. This shows that clomiphene does not induce FRP production. Thus, the diZerega reference does not describe, teach, nor suggest a material having the unique characteristics of the claimed invention. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §103 based on diZerega is respectfully requested.

In view of the foregoing, the Appellant urges that the Board reverse the 35 USC §102/103 rejections and that this application be passed to issuance.

Respectfully submitted,



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VIII. CLAIMS APPENDIX

Claims pending after final Amendment dated September 10, 2004

1 (Previously presented). An endogenous material, inducible in a mammal post-oestrus by clomiphene, and having the ability to reduce the mass of body organs including non-gonadal organs, of a live adult mammal, the material being obtained by:

collecting ovarian venous blood from a female mammal post-oestrus;

preparing ovarian venous plasma from the blood; and

at least partially purifying said material from the plasma to obtain at least a nominal 10-30 kD sub-fraction.

2 (Canceled).

3 (Previously presented). The material according to claim 1, wherein the purifying comprises obtaining a 10-20 kD fraction.

4 (Previously presented). The material according to claim 3, wherein the purifying additionally comprises ion exchange chromatography, and collecting the fraction eluted in 0.1-0.2 M NaCl.

5 (Previously presented). The material according to claim 1, wherein the purifying comprises the following protocol:

clearing plasma by centrifugation;

spinning the cleared plasma to give a nominal 0-30 kD fraction;

spinning the nominal 0-30 kD fraction to give the nominal 10-30 kD sub-fraction;

concentrating and gel-filtering the nominal 10-30 kD sub-fraction to give a nominal 10-20 kD sub-fraction;

concentrating and buffer-diluting the nominal 10-20 kD sub-fraction repeatedly;

applying the concentrate and buffer-diluted nominal 10-20 kD sub-fraction repeatedly to an ion exchange column eluted with a gradient of 0-.3 M NaCl; and

dividing the eluate into 0-0.1 M, 0.1-0.2 M and 0.2-0.3 M NaCl ion exchange fractions.

6 (Previously presented). The material according to claim 1, wherein the mammal is a sheep.

7 (Canceled).

8 (Previously presented). A pharmaceutical composition comprising an endogenous material inducible by clomiphene, having the ability to reduce the mass of body organs including non-gonadal organs, the material being obtained by:

collecting ovarian venous blood from a female mammal;

preparing ovarian venous plasma from the blood; and

at least partially purifying said material from the plasma to obtain at least a nominal 10-30 kD sub-fraction

and a pharmaceutically acceptable excipient or carrier.

9 (Canceled).

10 (Canceled).

11 (Previouly presented). The pharmaceutical composition, according to claim 8, wherein the purifying comprises obtaining the 10-20 kD fraction.

12 (Previously presented). The pharmaceutical composition, according to claim 8, wherein the purifying additionally comprises ion exchange chromatography, and collecting the fraction eluted in 0.1-0.2 M NaCl.

13 (Previously presented). The pharmaceutical composition, according to claim 8, wherein the purifying comprises the following protocol:

clearing plasma by centrifugation;

spinning the cleared plasma to give a nominal 0-30 kD fraction;

spinning the nominal 0-30 kD fraction to give the nominal 10-30 kD sub-fraction;

concentrating and gel-filtering the nominal 10-30 kD sub-fraction to give a nominal 10-20 kD sub-fraction;

concentrating and buffer-diluting nominal 10-20 kD sub-fraction repeatedly;

applying the concentrated and buffer-diluted nominal 10-20 kD sub-fraction repeatedly to an ion exchange column eluted with a gradient of 0-.3 M NaCl; and

dividing the eluate into 0-0.1 M, 0.1-0.2 M and 0.2-0.3 M NaCl ion exchange fractions.

14 (Previously presented). The pharmaceutical composition, according to claim 8, wherein the mammal is a sheep.

15 (Withdrawn). A method for treating organ or tissue hypertrophy wherein said method comprises administering, to a patient in need of such treatment, an effective amount of an endogenous material, inducible by clomiphene, having the ability to reduce the mass of body organs including non-gonadal organs, the material being obtained by:

collecting ovarian venous blood from a female mammal;

preparing ovarian venous plasma from the blood; and

at least partially purifying said material from the plasma to obtain at least a nominal 10-30 kD sub-fraction.

16 (Canceled).

17 (Withdrawn). The method, according to claim 15, wherein the purifying comprises obtaining the 10-20 kD fraction.

18 (Withdrawn). The method, according to claim 15, wherein the purifying additionally comprises ion exchange chromatography, and collecting the fraction eluted in 0.1-0.2 M NaCl.

19 (Withdrawn). The method, according to claim 15, wherein the purifying comprises the following protocol:

clearing plasma by centrifugation;

spinning the cleared plasma to give a nominal 0-30 kD fraction;

spinning the nominal 0-30 kD fraction to give the nominal 10-30 kD sub-fraction;

concentrating and gel-filtering the nominal 10-30 kD sub-fraction to give a nominal 10-20 kD sub-fraction;

concentrating and buffer-diluting the nominal 10-20 kD sub-fraction repeatedly;

applying the concentrated and buffer-diluted nominal 10-20 kD sub-fraction repeatedly to an ion exchange column eluted with a gradient of 0-.3 M NaCl; and

dividing the eluate into 0-0.1 M, 0.1-0.2 M and 0.2-0.3 M NaCl ion exchange fractions.

20 (Withdrawn). The method, according to claim 15, wherein the mammal from which the ovarian venous blood is collected is a sheep.

21 (Withdrawn). The method, according to claim 15, wherein the patient is in need of treatment for the group consisting of prostatic hypertrophy, cardiac hypertrophy, polycystic ovarian syndrome, endometriosis, polycystic renal disease, and pituitary adenoma.

IX. EVIDENCE APPENDIX

Declaration of Iain James Clarke Under 37 CFR §1.132 dated July 26, 2004 (attached)

Declaration of John Ernest Hart Under 37 CFR §1.132 dated August 2, 2004 (attached)

Declaration of John Ernest Hart Under 37 CFR §1.132 dated July 18, 2003 (attached)

X. RELATED PROCEEDINGS APPENDIX

There are no related proceedings

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Vera Afremova
Art Unit	:	1651
Applicant	:	Hart, John Ernest
Serial No.	:	09/856,944
Filed	:	July 16, 2001
For	:	Isolated Material Having an Anti-Organomorphic Effect

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF DR JOHN ERNEST HART UNDER 37 CFR a1.132

Sir:

1. I am the inventor of the invention described in the above patent application.

2. I received a BSc in Zoology from the University of Sheffield in 1975 and I received a PhD in Biochemistry from the University of Surrey, Guildford, UK, in 1981.

3. The major part of my career in biochemistry has involved the identification and elucidation of hormones in humans and animals.

4. I have read and understand the patent application serial number 09/856,944 for my invention, and I have read and understand the cited references, i.e. Hart and US 4,734,398 (diZerega). The following statements recite facts evident from those respective documents.

5. The patent application relates to a compound which I will refer to as "Micrin". Micrin, which is naturally occurring, is obtainable from the blood of sheep. Micrin is inducible by the non-endogenous, synthetic compound clomiphene. Micrin is also obtainable from sheep, even when those sheep are not treated with clomiphene, as explained in the patent application.

6. Micrin is present in a plasma fraction having a nominal cutoff of 10,000 - 20,000 daltons. Clomiphene has a molecular weight below 500.

7. diZerega discloses "Follicular Regulating Protein" (hereinafter FRP). FRP is only detectable immediately downstream of an ovary which is just about to ovulate, and is not

concurrently detectable downstream of the contralateral anovulatory ovary. Micrin is detectable six-days post-oestrus (i.e. post-ovulation), downstream of both ovaries, concurrently. FRP is not detectable in anovulatory individuals. Micrin is detectable in anovulatory individuals. FRP is not detectable in peripheral blood. Micrin is detectable in peripheral blood.

8. Micrin activity is detectable in blood plasma at a time (after ovulation) and from places (downstream of anovulatory ovaries and from peripheral blood) when and where FRP activity is not detectable (diZerega, Example One, Column 8-12, notably Column 10, lines 52-60 and Column 11, lines 61-66).

9. FRP is exclusively ovarian in origin: it is secreted by granulosa cells in the ovary (see Column 11, lines 55-60 and Column 28, line 65). Micrin is produced by the ovaries and testes, and by other organs.

10. FRP inhibits gonadotropin action in the ovary. FRP therefore suppresses gonadotropin-induced regrowth of juvenile rat ovaries previously shrunken by hypophysectomy. Micrin reduces, in normal adult female rats, the masses of organs such as the heart and kidneys which are uninfluenced by gonadotropins and remote from the ovaries. It is unlikely that FRP has a downregulatory effect on such organs as the heart and kidneys, since it is an intra-ovarian gonadotropin inhibitor which does not appear in peripheral blood.

11. I infer from Fig. 18 of diZerega that FRP is not induced by clomiphene.

12. For FRP there are described potential uses in contraception and infertility. Micrin is useful in the treatment of general organ or tissue hypertrophy.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed: John Hart

Dr. John E Hart

Date: 18th July 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Vera Afremova
Art Unit	:	1651
Applicant	:	HART, John Ernest
Serial number	:	09/856,944
Filed	:	July 16, 2001
For	:	Isolated Material Having an Anti-Organotrophic Effect

Assistant Commissioner for Patents
Washington, D. C. 20231

DECLARATION OF DR JOHN ERNEST HART UNDER 37 CFR S. 1.132

1. I am the inventor of the invention described in the above patent application. This Declaration supplements my previous Declaration dated 18 July 2003.

2. I have studied the Office Action sent by the examiner on 13 May 2004. This Declaration is intended to clarify some of the distinctions between the present invention and the cited reference US 4 734 398 (diZerega), which I have read and understood.

3. The compound disclosed by diZerega, "follicular regulating protein" or FRP, does not reduce ovarian mass; exogenous FRP only inhibits the regrowth of juvenile ovaries pre-shrunk by hyophysectomy and then boosted by gonadotropins.

4. What can be predicted to be the likely effect of **endogenous FRP** on ovarian mass in normal intact adults?
Since FRP is only produced in the preovulatory phase, an action at that time only can be posited, and then only on the ovulating ovary, the site of FRP production, no FRP being present in the peripheral circulation. Endogenous gonadotropins increase ovarian mass mid-cycle in adult mammals. Hence, endogenous FRP might blunt this mid-cycle rise in the mass of the ovulating ovary. But there are no grounds for predicting a reduction in the absolute mass of the ovulating ovary or any effect on the mass of the non-ovulating ovary.

5. What if **exogenous FRP** were given to intact adult mammals, rather than hypophysectomised juvenile animals - would that cause an absolute reduction in ovarian mass?
No. All this might achieve would be a blunting of the mid-cycle rise in the mass of the ovulating ovary, given that the mode of action of FRP is to inhibit gonadotropin action. The potential suppression of a rise in mass of the ovulating ovary is not an absolute reduction in the mass of both ovaries, such as can be readily obtained with exogenous micrin.

6. Would the administration of **exogenous FRP** to adult intact mammals be expected to cause an absolute reduction in **non-gonadal organ masses**, as is achieved with exogenous micrin?
Again, no. To say otherwise would be to imply that gonadotropins increase the mass of non-

gonadal organs, which is n[illegible]e case, and ignores the fact that FRP do[illegible]ot even reduce in an absolute sense the mass of an ovulatory ovary; diZerega makes it clear (for example column 11, lines 55-66) that the effect of FRP is to suppress the response to gonadotropins.

7. FRP and micrin are demonstrably separate entities, having no connection whatsoever.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed: 

Dr John Ernest Hart

Date: 2 August 2004

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26th July 2004

Applicant : HART, John Ernest
Serial number : 09/856,944

Assistant Commissioner for Patents
Washington, D. C. 20231

DECLARATION OF PROFESSOR IAIN JAMES CLARKE UNDER 37 CFR S. 1.132

1. My name is Iain James CLARKE and I am currently Senior Principal Research Fellow at Prince Henry's Institute of Medical Research, Clayton, Victoria, Australia, conducting research in the field of neuroendocrinology. I am also Honorary Professor, Department of Physiology, Monash University, Clayton, Victoria, Australia and Director of Biological Resources of Prince Henry's Institute.

2. I received a B.Agric.Sci from Massey University in 1971 and a M.Agric.Sci from the same Institution in 1973. I received a PhD in animal reproduction, endocrinology and behaviour in 1977 from Edinburgh University, the work having been completed in the Medical Research Council Unit of Reproductive Biology. I was appointed to my present post as Senior Principal Research Fellow in 1998.

3. The major part of my career has been in the field of reproductive endocrinology, generally involving the elucidation of the properties and behaviour of hormones in animals. I have published 350 papers or chapters in learned journals or books and I am a member of the Endocrine Society of the US amongst other Societies. I am Program Organising Chairman for the International Neuroendocrine Federation and am active in the organisation of other meetings around the Globe. An example of my international standing is my recent paper presented to The Endocrine Society in the TransPacific Symposium of this year's meeting.

4. I have carried out research on ovulation in sheep and humans, as evidenced in the following papers:-

CLARKE, I.J., SCARAMUZZI, R.J. and SHORT, R.V. Ovulation in prenatally androgenized ewes. J. Endocrinol. 73: 385-389, 1977.

VAN LOOK, P.F.A., CLARKE, I.J., DAVIDSON, W. and SCARAMUZZI, R.J. Ovulation and lambing rates in ewes actively immunized against androstenedione. J. Reprod. Fert. 53: 129-130, 1978.

CLARKE, I.J., FRASER, H.M. and Mc NEILLY, A.S. Active immunization of ewes against luteinizing hormone releasing hormone, and its effects on ovulation and gonadotrophin, prolactin and ovarian steroid secretion. J. Endocrinol. 78: 30-47, 1978.

SCARAMUZZI, R.J., BAIRD, D.T., CLARKE, I.J., MARTENSZ, N.D. and VAN LOOK, P.F.A. Ovarian morphology and the concentration of steroids during the oestrous cycle of sheep actively immunized against androstenedione. J. Reprod. Fert. 58: 27-35, 1980.

CARSON, R.S., FINDLAY, J.K., CLARKE, I.J. and BURGER, H.G. Estradiol, testosterone and androstenedione in ovine follicular fluid during growth and atresia of ovarian follicles. Biol. Reprod. 24: 105-113, 1981.

HURLEY, D.M, BRIAN, R, CLARKE, I.J. and BURGER, H.G. Induction of ovulation with subcutaneous pulsatile gonadotropin-releasing hormone: singleton pregnancies in patients with previous multiple pregnancies after gonadotropin therapy. Fertil. Steril. 40: 575-579, 1983.

KEOGH, E.J, MEAKIN, J.L, BANOVIC, S, CURNOW, D.H, GILES, P.F.H, CLARKE, I.J. and WILSON, D. Ovulation induction with pulsatile gonadotrophin releasing hormone (GnRH). Clin. Reprod. Fert. 2: 175-189, 1983.

CLARKE, I.J, WRIGHT, P.J, CHAMLEY, W.A. and BURMAN, K. Differences in the reproductive endocrine status of ewes in the early post-partum period and during seasonal anoestrus. J. Reprod. Fert. 70: 591-597, 1984.

HURLEY, D.M, BRIAN, R, OUTCH, K, STOCKDALE, J, FRY, A, HACKMAN, C, CLARKE, I. and BURGER, H.G. Induction of ovulation and fertility in amenorrheic women by pulsatile low-dose gonadotropin-releasing hormone. New Eng. J. Med. 310: 1069-1074, 1984.

DRIANCOURT, M.A, FRY, R.C, CLARKE, I.J. and CAHILL, L.P. Follicular growth and regression during the 8 days after hypophysectomy in the sheep. J. Reprod. Fert. 79: 635-641, 1987.

HYLAND, J.H, WRIGHT, P.J, CLARKE, I.J, CARSON, R.S, LANGSFORD, D.A. and JEFFCOTT, L.B. Infusion of gonadotrophin-releasing hormone (GnRH) induces ovulation and fertile oestrus in mares during fertile oestrus. J. Reprod. Fert. Suppl. 35: 211-220, 1987.

FRY, R.C, CLARKE, I.J, CUMMINS, J.T, BINDON, B.M, PIPER, L.R. and CAHILL, L.P. Induction of ovulation in chronically hypophysectomized Booroola ewes. J. Reprod. Fert. 82: 711-715, 1988.

McNATTY, K.P, HENDERSON, K.M, FLEMING, J.S, CLARKE, I.J, BINDON, B.M, PIPER, L.R, O'SHEA, T, HILLARD, M.A. and FINDLAY, J.K. The physiology of the Booroola Ewe and Ram. 2nd International Workshop on Major Genes for Reproduction in sheep, Toulouse, France, Ed INRA Paris. pp 105-124, 1991.

FINDLAY, J.K, CLARKE, I.J, LUCK, M.R, RODGERS, R.J, SHUKOVSKI, L, ROBERTSON, D.M, KLEIN, R, MURRAY, J.M, SCARAMUZZI, R.J, BINDON, B.M, O'SHEA, T, TSONIS, C.G. and FORAGE, R.G. Peripheral and intragonadal actions of inhibin related peptides. J. Reprod. Fert. Supplement 43: 139-150, 1991.

In particular, I have carried out work that investigated similar principles to those expounded by diZerega, as indicated in the following publication:-

CAHILL, L.P, CLARKE, I.J, CUMMINS, J.T, DRIANCOURT, M.A, CARSON, R.S. and FINDLAY, J.K. An inhibitory action at the ovarian level of ovine follicular fluid on PMSG-induced folliculogenesis in hypophysectomized ewes. Proc. 5th Ovarian Workshop (Laramie), Eds. D.O. Toft and R.J. Ryan, pp 35-38, Ovarian Workshops, Champaign, Ill. 1985.

I have carried out work on endocrinology of tamoxifen (which, like clomiphene is a triphenylethylene derivative with antiestrogenic properties) as outlined in the following publication:-

CLARKE, I.J. Effects of tamoxifen on plasma concentrations of luteinizing hormone and follicle-stimulating hormone in ovariectomized ewes. J. Endocrinol. 99: 23-29, 1983.

More recently I have carried out research on the compound referred to as "micrin" and described in the above patent application.

5. I have studied the Office Action sent by the examiner on 13 May 2004. I have also read and understood the cited reference US 4 734 398 (diZerega) and I was already familiar with diZerega's work, as indicated above.

6. Clomiphene is known to induce ovulation, if provided over a prolonged period of time, in women who are not ovulating. However, if sheep are provided with an acute administration of clomiphene within a few days after ovulation has occurred, as is described in the present patent application, this certainly does not cause further ovulation. The reproductive system is refractory to re-ovulation induction at this time, because the sheep would be in the luteal phase of the oestrous cycle, when progesterone levels are high; this prevents ovulation.

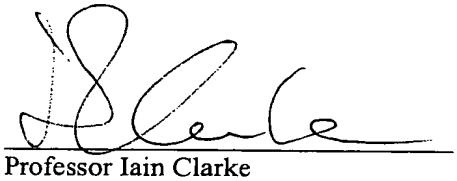
7. Indeed, clomiphene acts as a pure oestrogen in the sheep, at least at the level of the hypothalamo-pituitary axis. I have unpublished data to this effect. It is therefore probable that clomiphene would not induce ovulation in a sheep under any circumstances.

8. On the other hand, clomiphene does appear to induce the production of micrin, at whatever phase of the oestrous cycle it is administered. Micrin induction by clomiphene does not appear to be a secondary effect of ovulation, as it occurs whenever clomiphene is administered and regardless of when ovulation has occurred.

9. From my own immunohistochemistry experiments I have found that micrin can be found in brain tissues. This strongly suggests that that micrin is different from the compound described by diZerega.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed: 

Professor Iain Clarke

Date: 26 July 2004